

ANIMAL GROWTH, DEVELOPMENT, & NUTRIENT UTILIZATION

Panel Manager – Dr. Terrence M. Bradley, University of Rhode Island

Program Director – Dr. Debora L. Hamernik

Research in this program area contributes to our understanding of the biological mechanisms underlying growth and development in agriculturally important animals. Emphasis is placed on innovative approaches in several research areas including, but not limited to: cell proliferation and differentiation; genetic mechanisms underlying growth and development; metabolic regulators such as growth factors; synthesis and degradation of protein and lipid at the cellular or tissue level; metabolic and nutritional aspects of growth and development including rumen microfloral development and cellular and molecular aspects of the effect of environmental stress on growth and development; mechanisms controlling nutrient digestion, absorption and availability; and *in vivo* modification of animal products to enhance nutrient composition for human consumption. Development of dynamic modeling systems assessing specific quantitative estimates of nutrient requirements is also encouraged.

2000-03280 Growth and Development of Chicken Muscle

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Grant 00-35206-9427 \$185,000; 2 years

The goal of this project is to understand the mechanisms responsible for the formation of diverse types of muscle in developing chickens and quail. This proposal focuses on understanding muscle formation during the embryonic period of chicken and quail development, the time when all the muscles of the bird are first formed. A major muscle protein, myosin heavy chain (MyHC), will be investigated to determine what controls the temporal appearance of individual forms MyHCs. These forms of myosin control the contraction of muscles, its major protein content, and determine whether the meat obtained from the muscle is either “white” or “dark”. The studies will determine the actions of the nervous system and other hormonal agents that mediate muscle formation and function; in particular whether the nervous system influences the forms of myosin that a forming muscle contains. Embryonic surgery, *in situ* hybridization, and immunohistochemistry will be used to measure these effects. These experiments have important implications for the formation of muscles of differing functional types that could be useful in improved production efficiency of chicken and quail muscle in conventional breeding programs. Understanding factors that can alter muscle fiber types and fiber growth could provide a genetic basis for control of meat production.

2000-01100 Production of Monoclonal Antibodies against Porcine Myostatin

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Seed Grant; Grant 00-35208-9418; \$50,000; 2 Years

Myostatin is a recently identified molecule that appears to be involved in the regulation of skeletal muscle growth. Using gene knock-out technology in mice to inhibit expression of the myostatin gene, muscle size increased 2-3 times compared to ordinary mice. Thus, it has been suggested that myostatin functions to suppress skeletal muscle growth. The discovery of myostatin may help the livestock industry to efficiently produce lean meat for the American consumer. If it can be shown that myostatin acts as a suppressor for skeletal muscle growth in newborn and growing animals, then blocking the biological action of myostatin in neonatal or growing animals should improve the growth potential of skeletal muscle, and thus produce meat animals with more lean muscle and less fat. One potential approach to block the biological activity of myostatin is to develop anti-myostatin antibodies that block biological activity of myostatin. Antibodies against a biological molecule are valuable tools to study the physiological, biochemical, and cellular role of the molecule. Therefore, the objective of this proposal is to produce monoclonal anti-porcine myostatin antibodies. The monoclonal antibodies produced in this

project will be important in testing the potential of anti-myostatin antibodies as a tool for improving skeletal muscle growth, and thus the lean composition in meat. In addition, the monoclonal anti-myostatin antibodies will contribute to the investigation of the mechanism of action of myostatin in regulating skeletal muscle growth.

2000-03300 Impact of IGF-1 Overexpression in Pig Mammary on Lactation and Piglet Intestine

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Grant 00-35206-9537; \$300,000; 3 Years

The pre-weaning period constitutes a critical phase in pork production as this period represents the time of greatest animal morbidity and mortality. The 1991 USDA National Swine Survey on Morbidity/Mortality and Health Management of Swine in the U.S. estimated that overall, pre-weaning mortality was 15%, that nearly all cases of morbidity and mortality occurred in piglets ≤ 7 days of age and that 58% of the cases of morbidity were reportedly due to scours and 30% of the mortality was attributed to scours or starvation. Thus, improving pre-weaning growth performance, through improved sow milk production, could have important economic significance for U.S. agriculture. Our long-range goal is to optimize swine lactation performance and piglet growth and development through the targeted overexpression of milk proteins in the porcine mammary tissue. To this end, we have developed lines of transgenic swine that overexpress the multi-functional milk protein, insulin-like growth factor (IGF-1) in milk. The objective of this application is to investigate the impact of mammary overexpression of IGF-1 on the maternal and neonatal outcomes. Two aims are proposed to determine the impact of mammary IGF-1 overexpression on: 1) the mammary IGF-1 and IGF receptor expression, mammary growth, mammary nutrient uptake, and milk composition and yield in swine, and 2) piglet intestinal development, digestive function and the intestinal IGF axis. The proposed research is innovative because it involves a novel approach to improving piglet growth and development.

2000-03246 Porcine Muscle Satellite Cell Recruitment

Grant, A.L.; Gerrard, D.E.

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Grant 00-35206-9414; \$120,000; 2 Years

Until mechanisms responsible for regulating muscle protein deposition during growth of meat animals are more clearly understood, improving efficiency of meat production will continue being a challenge for the agricultural industry. Perturbation of muscle satellite cell growth is likely responsible for the decreased rate of postnatal muscle growth that occurs in the mid to late stages of growth, and contributes to inefficiency of meat production. It is unclear how satellite cell activity can be maintained to enhance muscle growth at the expense of fat deposition, especially in the later stages of growth prior to market weight. The overall objective of this project is to determine how to up-regulate satellite cell recruitment so that muscle growth can be enhanced. The central hypothesis is that growth factor (HGF- and IGF-I)-induction of satellite cell recruitment can enhance muscle growth and partially prevent the decrease in muscle growth rate that occurs as pigs approach market weight. We plan to test this hypothesis with the following specific objectives: 1) determine how satellite cell activity is regulated at various stages of muscle fiber growth, and 2) determine how satellite cell activity can be increased for enhancing muscle hypertrophy. As an outcome of the proposed investigations described in this application, we expect to determine the cellular processes limiting muscle growth. Consequently, new strategies may be formulated that will minimize decreased efficiency of muscle protein deposition in growing meat animals, resulting in reduced production costs and increased competitiveness of animal protein in global markets.

2000-03249 Arginine-Specific Mono-ADP-Ribosylation in Embryonic Skeletal Muscle

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Grant 00-35206-9381; \$90,000; 1 Year

The overall goal of this project is to understand the function of a specific cellular chemical reaction, ADP-ribosylation, in regulating embryonic development and growth of skeletal muscle. This reaction involves the addition of a chemical group (ADP-ribose) to an amino acid side chain (an arginine) of a protein, which alters the properties and function of the modified protein. Such protein modifications are one mechanism that cells use as to regulate function or transmit intracellular signals. This reaction is catalyzed by enzymes known as ADP-ribosyltransferases, or ARTs, and the reverse reaction is catalyzed by a specific hydrolase. At least three different ART enzymes have been identified in muscle. We have previously shown, using an inhibitor, that this reaction is necessary for proper embryonic development of muscle cells grown in culture. In this project, two approaches will be used to understand the specific function of the ART enzymes and to determine which one plays a crucial role in muscle development. First, we will determine where each of the ART enzymes is located in the cells of developing and adult muscles. Antibodies that specifically recognize each ART and the hydrolase will be prepared and used to localize the enzymes by fluorescence microscopy. Second, we will use molecular biology techniques to alter the amount of each of the enzymes in muscle cells grown in culture, to examine the individual function of each. Results of these studies will provide new information about the basic cellular mechanisms that control growth of skeletal muscle in animals.

2000-03268 Nutritional Regulation of Pancreatic alpha-Amylase in Ruminants

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Strengthening Award; Grant 00-35206-9380; \$160,000; 2 Years

While ruminants have evolved as users of dietary fiber, modern production practices depend principally on starch as a major supplier of dietary energy. Because of this, ruminants may not possess the appropriate complement of digestive enzymes necessary to optimize the digestibility of dietary carbohydrate. The enzyme responsible for the initial breakdown of starch in the small intestine is pancreatic alpha-amylase. Because of the evolutionary differences in the feeding habits of ruminants, it is unclear if adequate alpha-amylase is secreted when high starch diets are fed to ruminants. Experiment 1 seeks to determine how nutrients, specifically carbohydrate and protein, interact to affect alpha-amylase secretion. Experiment 2 seeks to determine what cellular mechanism(s) is responsible for these changes. By comparison of results from Experiments 1 and 2, the relationship between pancreatic alpha-amylase secretion and production and dietary nutrient supply will be elucidated. Ultimately, knowledge gained from these experiments will be used to devise feeding strategies that enhance pancreatic secretion of alpha-amylase activity and, therefore, improve small intestinal starch digestion efficiency. Approximately 20 million metric tons of starch are fed to an estimated 22 million cattle in U.S. feedlots. An improvement in small intestinal starch digestive efficiency of only 1% would result in an estimated savings of over \$5 million annually to the beef industry alone.

2000-01986 Student and Post-Doc Travel Support for the International Congress on the Biology of Fish

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Conference Grant; Grant 00-35206-8960; \$10,000; 9 Months

Funds from this grant will be used to support travel costs of students and postdoctoral fellows to attend The International Congress on the Biology of Fish on the campus of the University of Aberdeen, Scotland, UK from July 23-27, 2000. This is the fourth in a series of international meetings on the

physiology and organismal biology of fish. The focus of these meetings has been communication of basic knowledge of fish physiology and organismal biology and implications for management and culture of fish. This is a unique meeting that focuses on fundamental new research in the biology of fish and how it can be used to address societal and environmental issues such as fish culture, pollution and endangered species. The meeting is attended by the top fish physiologists and organismal biologists around the world. Past meetings have been extremely successful, with high quality of presentations on a wide variety of topics. Some symposia within the meeting have been published in journals (e.g., Comparative Biochemistry and Physiology) and all have been published as books available to attendees. The books contain either extended abstracts or short papers; thus, providing substantial "take home" information to the attendees. Prior meetings have been held in North America and each meeting has attracted more than 200 speakers from over 40 countries. In an attempt to further increase the "international" aspects of the meeting, the next International Congress on the Biology of Fish will be held in Aberdeen, Scotland in July, 2000. Candidates will be judged based on a combination of the scientific quality of their abstract, relevance to the sessions of the meeting, and financial need.

2000-03260 The Control of Skeletal Muscle Growth and Development in the Tilapia *Oreochromis mossambicus*

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Grant 2001-35206-10078; \$185,000; 2 Years

In mammals, skeletal muscle growth and development are negatively regulated by a protein appropriately named myostatin (MSTN). Mice which lack MSTN or cattle that possess mutant forms of this gene product have individual muscle fibers that are 200-300% larger than fibers from normal animals. I have successfully isolated and characterized MSTN clones from two commercially important finfish: the tilapia *Oreochromis mossambicus* and the white bass *Morone chrysops*. Understanding the molecular, biochemical and physiological actions of this growth inhibitor will help aquaculturists to avoid the conditions which favor increased MSTN production and consequently, reduced skeletal muscle growth. In addition, data from these studies will provide the basis for the genetic manipulation of tilapia MSTN and the production of "double muscled" fish. The long-term goals of the proposed studies are to determine (i) how MSTN influences the growth and development of tilapia skeletal muscle and (ii) whether MSTN gene expression is influenced by stressors frequently encountered when culturing tilapia. These goals will be accomplished by meeting three objectives. In the Objective 1 studies, we will determine the developmental and tissue-specific expression pattern (i.e. when and where it occurs) of tilapia MSTN in developing larvae. In the Objective 2 studies, we will determine how tilapia MSTN influences skeletal muscle growth processes by culturing skeletal muscle slices in the presence of recombinant or synthesized MSTN. In the Objective 3 studies, we will determine whether the gene expression of tilapia MSTN is altered by fasting, stocking density, restraint stress or by salinity changes.

2000-03236 Stem Cell Biology of the Prepubertal Ruminant Mammary Gland

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Postdoctoral Fellowship; Grant 00-35206-9535; \$89,945; 2 Years

The cost of replacing cattle that die or are culled from American dairy herds exceeds \$4 billion per year. Optimizing the growth of replacement heifers is essential to maximize the return on this large investment. It is also critical that we understand factors involved in prepubertal mammary development because excessive heifer growth rates can reduce mammary growth. Furthermore, because milk yield is directly related to the number of secretory cells in the mammary gland, reduced prepubertal mammary development can permanently decrease the milk yield and profit potential of the heifer. Therefore, the focus of this postdoctoral fellowship proposal is to investigate the growth and development of the prepubertal ruminant mammary gland. Detailed microscopic analyses will be used to localize and

quantify the proliferation of mammary epithelial cells to determine how each of the mammary cell types contributes to mammary development. Analyses of cell death during prepubertal ruminant mammary development will also be conducted because cell death has been shown to play an important role in mammary development in rodents. Currently, the importance of cell death during ruminant mammary development is unknown. Data from the previous analyses will be incorporated into three-dimensional reconstructions of histologic sections to generate a model for mammary development in the prepubertal ruminant mammary gland. The results of these analyses will provide critical insight into the cell types and processes involved in ruminant mammary development. This information will aid in the development of therapies that improve prepubertal mammary development and increase the return on investment in replacement heifers.

2000-03269 Optimization of Phytate-Phosphorus Hydrolysis in Broiler Diets

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Grant 00-35206-9360; \$200,000; 3 Years

Environmental issues have focused producer, legislative, and public attention on optimizing animal waste management. New legislation limits the amount of manure phosphorus that may be applied to soil. To maximize manure application rates and prevent environmental pollution, plant (phytate-phosphorus) utilization by animals must be maximized and diet supplementation with supplemental mineral based (inorganic) phosphorus minimized. Plant based phosphorus is highly unavailable to poultry and swine and is also an anti-nutrient in that it negatively influences the ability of these animals to utilize minerals such as zinc and calcium. Use of calcium forms in the diet that deliver calcium to the animals but minimize the negative interaction between plant based phosphorus and calcium may result in improved use of the plant phosphorus and of the calcium. Optimization of the use of enzymes such as phytases, cellulases, and proteases and changes in feed formulation (use of different calcium sources) that may help the animal better utilize phosphorus of plant origin could result in a large (greater than 60%) decrease of phosphorus in poultry litter. The specific objectives of this work are: 1) Develop an enzymatic mix that optimizes the release of plant phosphorus based on a digestion simulation assay, 2) Determine the effect of calcium form on plant phosphorus release, and 3) Apply 1 and 2 in broilers and determine the extent of plant phosphorus use.

2000-03264 Mechanism of Milk-lipid Secretion

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Grant 00-35206-9428; \$210,092; 3 Years

Experiments are designed to test the hypothesis that butyrophilin (BTN), an abundant protein in the milk-fat-globule membrane, is essential for the regulated secretion of lipid droplets from mammary cells. Under current funding from the U.S.D.A., we have tested this possibility directly by ablating the BTN gene in mice. As predicted, 'knock-out' of BTN in homozygous animals (-/-) profoundly disrupts milk secretion. Large pools of lipid accumulate in the cytoplasm and droplets escape from the cell without an intact membrane envelope. To firmly establish the function of BTN in lactation, we will characterize the phenotype of the BTN (-/-) mouse by comparing milk composition, mammary gland morphology and mammary development in wild-type (+/+), hemizygous (+/-), and knock-out (-/-) animals. Under a separate aim, we will determine whether the domains of BTN that are on the external, or internal surface of the cell are essential for function. Membrane-anchored forms of BTN that lack either the external or internal domains of the protein will be expressed from recombinant adenoviruses to see if they restore regulated milk secretion in (-/-) mice. The BTN gene is the first gene to be identified that appears to regulate the secretion of milk lipids. Increased understanding of this process should aid in attempts to manipulate the quality and amount of fat in milk, with economic benefits to dairy producers and health benefits to consumers.

2000-03266 Regulation of Growth Hormone Cell Differentiation During Chicken Development

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Grant 00-35206-9463; \$210,000; 2 Years

Understanding the mechanisms regulating growth and feed utilization in poultry are essential to develop new methods for improving performance, yield and the health of chickens raised for human consumption. This project focuses on the mechanisms controlling the differentiation of the cells during embryonic development that secrete growth hormone. This hormone controls growth and feed efficiency in animals. The overall goal of the research described in the current proposal is to improve growth characteristics in broiler chickens through improving our understanding of the regulation of growth hormone cell differentiation during late embryonic development. The specific objectives of this project are 1) Evaluate potential mechanisms for corticosteroid-induced growth hormone cell differentiation, 2) Determine somatostatin effects on growth hormone secretion and cell differentiation, and 3) Define involvement of the adrenal and thyroid glands in regulating growth hormone cell differentiation. The results of these studies should provide information directly applicable to the poultry industry to increase the efficiency of poultry production for human consumption.

2000-03323 Leptin Regulation of Bovine Mammary Cell Proliferation

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Grant 00-35206-9386; \$142,029; 2 Years

Our overall goal is to understand the mechanisms whereby high energy intake and increased body fat decrease growth of the mammary gland in young dairy heifers. Insulin-like growth factor-I (IGF-I) stimulates proliferation of mammary cells in culture. We hypothesize that leptin, a protein produced by fat tissues, inhibits IGF-I stimulation of mammary cells. In one series of studies, we will characterize the inhibitory effects of leptin on a bovine mammary cell line. We will vary incubation times to determine how rapidly IGF-I stimulates proliferation and how rapidly leptin inhibits it. We will determine if leptin can inhibit cells that are already stimulated and if preincubation with leptin inhibits IGF-I action. We will alter doses of leptin and IGF-I to determine if leptin inhibition can be overcome by a high IGF-I dose. In a second set of studies, we will use mammary cells taken directly from heifers before they reach puberty. We will determine if leptin inhibits IGF-I action in these cells and examine various doses and times for leptin and IGF-I action. These cells will proliferate in response to other hormones, and we will determine if leptin inhibits hormones other than IGF-I. These data will enable us to target specific mechanisms for leptin action in mammary cells in future studies. We expect the data to support the idea that leptin acts to specifically inhibit IGF-I stimulatory pathways. Understanding the regulation of mammary cell proliferation will form the basis for developing new nutritional, pharmacological, or transgenic approaches to increase the lifetime efficiency of US dairy cows.

2000-03271 Role of Porcine IGFBP-3 and -5 in Proliferation and Differentiation of Porcine Myogenic Cells

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Grant 00-35206-9342; \$210,000; 3 Years

The goal of our current proposal is to assess the insulin-like growth factor (IGF)-dependent and IGF-independent role of porcine insulin-like growth factor binding proteins (IGFBP)-3 and -5 in proliferation and differentiation of cultured embryonic porcine myogenic cells (PEMCs). It is well established that IGFs play a significant role in regulating proliferation and differentiation of embryonic muscle cells and that IGFBPs regulate the bioactivity of the IGFs. Data obtained during our current USDA grant establish that PEMCs produce IGFBP-3 and -5 and that IGFBP-3 mRNA and protein levels

are high in proliferating, nondifferentiated myogenic cells, drop dramatically (seven-fold) immediately prior to or during differentiation and increase after differentiation is complete. We believe that the unique changes in IGFBP-3 level during differentiation of PEMCs suggest that IGFBP-3 may play a role in differentiation in this system. In this proposal we have chosen to focus on the role of IGFBP-3 in proliferation and differentiation of PEMCs because IGFBP-3 is produced by these cells, IGFBP-3 levels vary dramatically during PEMC differentiation, and production of IGFBP-3 by PEMCs differs greatly from that observed in immortalized murine muscle cell lines. Additionally, we have shown that PEMCs produce IGFBP-5 and we will also assess this IGFBP's role in PEMC differentiation. Successful attainment of our goal will increase our fundamental understanding of the regulation of growth and differentiation of muscle tissue in an economically important, meat-producing species.

2000-03281 Growth Hormone Receptor 1A in Periparturient Dairy Cattle

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Grant 00-35206-9536; \$180,000; 2 Years

The change in nutrient metabolism that is required to support lactation in high producing dairy cattle is controlled by hormones that coordinate a variety of processes including the mobilization of fatty acids from adipose tissue and the synthesis of glucose from gluconeogenic precursors in liver. Growth hormone (GH or somatotropin) plays a central role in this process. The actions of GH in liver are mediated by the GH receptor (GHR). The long-term goal of our laboratory is to develop a management strategy for manipulating GHR expression that will facilitate the metabolic transition from late pregnancy to peak lactation in dairy cows. The objective of this application is to characterize the expression of one variant of the GHR (GHR 1A) and to determine if GHR 1A expression dictates the endocrine actions of GH during the periparturient period. Furthermore, we will determine if changes in feed intake affect GHR 1A expression. This research will test components of our model for GH-mediated nutrient partitioning in the liver of periparturient dairy cows. If our model is correct then we should be able to develop methods to increase GHR 1A expression in early postpartum cattle. By increasing GHR 1A we may be able to enhance the metabolic shift in liver function that is coordinated by GH. This should lead to a more rapid adaptation to the nutrient demands of lactation. The producer benefits because poor metabolic transitions associated with inadequate liver function are eliminated during early lactation and profits are increased through greater milk production.

2000-03289 Role of Compensatory Growth in Lactation

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Strengthening Award; Grant 2001-35206-10077; \$160,000; 3 Years

We have developed multi-step feeding regimens for growing animals which enhance mammary development and lactation potential. The basic idea of these regimens is to push energy at times when the animal can make the best use of it and to reduce energy levels when the animal is not as likely to put it to good use. Many livestock producers have been requesting information on the use of our regimen, but we feel that our multi-step regimen may be too complicated for most to implement without access to additional facilities and labor. A one-step gestational model may be more practical because producers can better manage animals during this phase. Our objectives are to determine if compensatory growth induced by our stair-step nutrition regimen once during gestation will enhance lactation potential and persistency for the first and subsequent lactation cycles by stimulating mammary cell growth and by inhibiting cell death. Using a rat model, we will investigate cell growth and death by immunohistochemical methods and gene expression analysis. Lactation persistency will be evaluated by litter weight and milk yield estimation. By establishing a link between nutritionally directed enhancement of lactation potential and mammary cell proliferation and death, we may be closer to controlling the lactation potential of dairy cattle. Understanding how cell number is controlled may lead to strategies for prolonging lactation, not

only by increasing peak yield, but also by reducing net loss of mammary cells, thereby increasing the persistency of lactation and the production efficiency.

2000-03242 Molecular Mechanisms Regulating IGFBP-3 Gene Expression in Mammary Epithelium
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Grant 00-35206-6428; \$185,000; 2 Years

Insulin-like growth factor-I (IGF-I) is a protein that regulates growth and development of the mammary gland. IGF-I stimulates the growth of mammary epithelial cells (MEC), the cell type that secretes milk. Increasing the number of secretory cells the gland possesses will increase the productive efficiency of the cow. IGF-I binds to specific proteins (IGFBP) that serve many functions. One of these is to regulate binding of IGF-I to its specific receptor on the cell membrane. Once IGF-I binds to its receptor, a complex network of signaling cascades are activated within the cell by enzymes that phosphorylate proteins. These molecules ultimately turn on genes that increase cell growth. IGFBP-3 increases the ability of IGF-I to increase cell growth in MEC. Both IGF-I as well as the intracellular signaling molecule cAMP stimulate IGFBP-3 synthesis and together these molecules activate the rate at which the IGFBP-3 gene is activated. One objective of this proposal is to identify the specific nucleotide sequences in the IGFBP-3 gene that turn the gene on in the presence of IGF-I and cAMP in bovine MEC. These sequences bind specific proteins (transcription factors) that activate genes. A second objective is to identify the signaling pathways that are activated within the cell by IGF-I and cAMP that result in the activation of the IGFBP-3 gene within the nucleus. The specific proteins that are activated by these factors will be identified. These studies will begin to unravel the complex regulation of the IGFBP-3 gene. This molecular approach will provide basic information on the physiological mechanisms that regulate mammary gland function. This fundamental knowledge will enable scientists to utilize new technologies to improve productive efficiency as well as animal well being.

2000-03259 Stress, Cell Death and the Remodeling of the Immature Fowl Adrenal Gland

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Grant 00-35206-9330; \$150,000; 2 Years

The adrenal gland produces corticosteroids that affect protein, carbohydrate and salt balance and immune function. Thus, the corticosteroids have a big impact on an animal's growth and resistance to disease. Stress can adversely affect these functions by causing the adrenal gland to secrete abnormal amounts or mixtures of these corticosteroids. One potential mechanism through which stress may alter the adrenal gland is by changing the composition of cells within the gland by killing off the normal resident population of cells and replacing them with new cells having different secretory characteristics. This hypothesis is the major thrust of the present investigation. In essence, this study will try to define how one kind of stress, dietary protein restriction, causes the death of normal cells and thus, remodels the adrenal gland to largely contain new cells having an altered function. Two major substances or hormones that control the adrenal gland are ACTH (adrenocorticotrophic hormone) and angiotensin II. ACTH appears to put a break on cell death while angiotensin II appears to enhance cell death. As it turns out, the death-promoting effect of angiotensin II appears to be enhanced by this stress. The present study will try to determine how the adrenal 'antennae' for these cell-death hormones, the ACTH and angiotensin II receptors, are changed by stress. This information may ultimately give rise to new ideas or methods to inhibit abnormal adrenal responses to stress. Optimizing adrenal function in the face of stress will have a salutary effect on animal growth and disease resistance.

2000-03261 Regulation and Action of Leptin in Periparturient Dairy Cows

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Grant 00-35206-9352; \$276,000; 3 Years

This proposal focuses on leptin, a recently discovered hormone synthesized by white adipose tissue. Emerging evidence from other species indicates that leptin plays a critical role in balancing the energy budget and in prioritizing the use of energy among key tissues in periods of nutritional deficit. However, factors regulating its synthesis and the nature of its actions have not been described in dairy cattle. Our overall goal is to demonstrate that the synthesis of leptin is regulated by energy balance in lactating dairy cows, and that leptin plays a role in the regulation of metabolism in early lactation. Three supporting objectives will be pursued. First, we will describe the temporal changes in the synthesis of leptin during the transition from late pregnancy to early lactation in high yielding dairy cows. Second, we will determine the role played by other hormones such as insulin in regulating changes in the synthesis of leptin. Third, we will study the actions of leptin on epithelial cells from the bovine mammary gland, a group of cells which accounts for a large fraction of energy expenditure and lipid synthesis in lactating dairy cows. These studies are timely and relevant because increased understanding of energy balance regulation in early lactating dairy cows offers unique opportunities to improve productivity, well-being and health. They will contribute to increased productivity and competitiveness of the US dairy industry by promoting the adoption of novel feeding and management strategies.

2000-03295 Characterization of cTAXREB, a Novel Gene Expressed in Muscle

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Grant 00-35206-9240; \$210,000; 2 Years

The formation of skeletal muscle occurs in several discrete stages including proliferation of the myoblast cells and fusion of these cells into the mature myocyte. This coordinated process of skeletal myogenesis is controlled in part by the actions of muscle-specific transcription factors. The myogenic regulatory factors (MRFs) represent a class of transcription factors that are absolutely required for expression of muscle genes. Moreover, optimal activity by the MRFs is achieved through interactions with additional coregulatory proteins. As such, the proteins associated with the MRFs may represent critical components necessary for the fine tuned control of muscle gene expression. In a screen for muscle regulatory genes, we have identified a gene with significant homology to the mammalian TAX response element binding protein 107 (TAXREB107). Northern analysis indicates the chick homolog (cTAXREB) is abundantly expressed in embryonic skeletal, cardiac and smooth muscle but is expressed at very low levels in adult muscle tissues. Because TAXREB107 is involved in transcriptional regulation and cTAXREB is expressed predominantly in muscle, we propose that the protein may function as a coregulator of muscle gene expression. To this end, we will examine the temporal and spatial expression of cTAXREB with regard to muscle-specific gene expression. In addition, we will examine the effects of mis-expression of wild-type, activating and inhibitory forms cTAXREB on embryonic chick skeletal muscle development. Completion of these experiments will improve our understanding of the molecular control of avian myogenesis and allow for the more effective design of strategies to improve muscle tissue deposition.

2000-03284 Gordon Research Conference on Mammary Gland Biology

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Conference Grant; Grant 00-35203-9422; \$5,000; 1 year

The goal of this project was to provide support for the biennial Gordon Research Conference on Mammary Gland Biology. This unique Gordon Conference, now in its 30th year (15th biennial session), brings together a diverse selection of scientists and clinicians to discuss the biology and pathology of the

mammary gland in a range of species including humans, laboratory, and domestic animals. Topics to be discussed with particular relevance to agricultural mammary biology include: epithelial stromal interactions in pubertal development of the mammary gland; cell cycle regulation in normal mammary development and tumorigenesis; mechanisms by which cross-talk between steroid hormones and growth factors is mediated; molecular regulation of galactosyl transferase and other enzymes of milk synthesis; the role of the mammary fat pad in mammatogenesis; the specialized response of the mammary stroma to ionizing radiation; adaptations of maternal lipid metabolism to the demands of lactation; and the biology of the epidermal growth factor families of receptors and ligands in mammary development.

2000-03267 Mechanism of Muscle Growth Stimulation by Somatotropin in Pigs

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Grant 00-35206-9405; \$210,000; 3 Years

It is important that meat producers find ways to increase the amount of meat they produce and to lower feeding cost. This can be accomplished by treating pigs with the hormone, somatotropin, which increases muscle mass, and at the same time, lowers the amount of food eaten. We have recently found that treatment of pigs with somatotropin increases growth primarily by increasing whole body protein synthesis in the fasting state and reducing whole body protein degradation in the fed state. We propose to determine whether the increase in protein synthesis that occurs in pigs treated with somatotropin is specific for muscle or whether it also occurs in other tissues in the body. We will also determine whether the higher rate of protein synthesis in somatotropin treated animals only occurs in the fasting state. To do this, we will trace the incorporation of amino acids into the protein of different tissues of the body of overnight fasted and fed pigs treated with somatotropin and controls. We also propose to determine the mechanism by which somatotropin stimulates protein synthesis. To do this, we will measure the amount and activity of the protein synthetic machinery in tissues by measuring the number of ribosomes and the activity of different factors which regulate the initiation of the translation of mRNAs into proteins in pigs treated with somatotropin and control pigs. These studies will be of potential use to swine producers by identifying the way that somatotropin promotes muscle growth.

2000-03314 Maternal n-3 Fatty Acid Supplementation to Enhance Brown Fat Thermogenesis in Lambs

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Grant 00-35206-9339; \$120,000; 2 Years

The physiological mechanisms regulating fetal growth and development, and neonatal adaptation to neonatal life, are complex and poorly understood in livestock species. At parturition, the newborn lamb encounters severe heat loss. Nonshivering thermogenesis of brown adipose tissue (BAT) is an important component for proper regulation of body temperature during the early neonatal period. Although our knowledge of the mechanisms controlling BAT thermogenic function in laboratory animals has advanced greatly in recent years, much less is known about these regulatory mechanisms in newborn ruminants. We propose that prenatal n-3 polyunsaturated fatty acid (PUFA) supplementation will enhance development of BAT in the fetus, thereby increasing the heat-producing capacity of BAT in newborn lambs. Experiment 1 will establish optimal levels of dietary fatty acids. The treatments will include a high saturated plus monounsaturated fatty acid (SMFA) diet or a high n-3 PUFA diet, fed at 2, 6, or 10% of the diet. Experiment 2 will document the role of adrenaline in the regulation of BAT degeneration in warm and cold environments. We propose that prenatal n-3 PUFA will: (i) enhance heat production by BAT in newborn lambs; and (ii) delay the degeneration of BAT in newborn lambs. This proposal is specifically designed to investigate the cellular and molecular aspects of the effects of cold versus warm exposure on BAT growth and development. If experimental findings support our hypothesis, maternal supplementation of n-3 PUFA will provide a strategy to enhance cold tolerance and improve survivability

of newborn ruminant animals.

2000-01166 High Performance Liquid Chromatography System for Multiple Users

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Equipment Grant; Grant 00-35208-9242; \$29,032; 1 year

The goal of this project is to obtain a state-of-the-art high performance liquid chromatography (HPLC) system for multiple users in the College of Agriculture and Life Sciences at the University of Vermont. HPLC is suitable for separating, purifying and quantifying many different biological compounds including carbohydrates, organic acids, proteins, amino acids, fatty acids, and nucleic acids. HPLC gives very high resolution, greater repeatability and shorter analysis times when compared to thin-layer or gel permeation chromatography. In combination with the appropriate detector system, HPLC provides superb quantification of the compound(s) of interest. A state-of-the-art HPLC system will be purchased that will give multiple users the ability to detect, quantify and purify compound(s) of interest to them. This equipment will augment existing infrastructure in research programs that represent a range from basic to applied science utilizing techniques in molecular, cellular and organismal biology. A state-of-the-art HPLC system will provide the investigators with an important and useful research tool and continue to build the research infrastructure of the College of Agriculture and Life Sciences at the University of Vermont.

2000-03251 Sterilization Vaccine for Cattle

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Grant 00-35206-9355; \$100,000; 2 Years

The goal of the project is to develop an immunization procedure to sterilize heifers and prevent pregnancy prior to entering the feedlot. The gene for the protein ovalbumin has been genetically engineered with seven gene inserts of a reproductive hormone, called LHRH, and is placed in a strain of bacteria which produces what is called a fusion protein. This protein, when purified and injected into heifers, induces antibody formation against ovalbumin and the LHRH. The vaccination neutralizes the LHRH hormone preventing ovulation and pregnancy in the heifer. The number of heifers going into feedlots each year in the United States is approximately 10 million. These heifers are docked on price paid to the producer for two reasons: 1) the female (heifer) does not grow as efficiently as the castrated male (steer) and 2) a variable percent of the heifers come into the feedlot pregnant. Pregnant heifers in feedlots are a management problem. Feeding a high concentrate ration to an animal to provide gain to a fetus that goes into the gut pile is expensive. Heifers are usually \$5 to \$10 per 100 weight lower in value than steers, and at least half of the decreased value is based on the potential that heifers are pregnant. This is an estimated \$25 loss per head on 10,000,000 head of heifers, or \$250 million per year. A sterilization vaccine would be a less traumatic and less stressful way to spay or castrate our livestock species in the future.